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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,248	02/14/2001	Carl P. Decicco	PH-7064 (BMS-0685)	1696

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EXAMINER

RUSSEL, JEFFREY E

ART UNIT

PAPER NUMBER

1654

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

8M

Office Action Summary**Application No.**

09/783,248

Applicant(s)

DECICCO ET AL.

Examiner

Jeffrey E. Russel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 4-78 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,4,5,19,47,51-56,60-64,68,72-74 and 78 is/are allowed.
- 6) ☒ Claim(s) 6-11,15,17,20-46,57-59,65-67,69-71,75 and 77 is/are rejected.
- 7) ☒ Claim(s) 12-14,16,18,48-50 and 76 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. <u>20040419</u> |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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1. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The disclosure is objected to because of the following informalities: The status of the U.S. patent application referred to in the paragraph beginning at page 92, line 1, of the specification, line 11 of the replacement paragraph filed March 18, 2004, should be updated. Appropriate correction is required.

2. Claims 7 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is indefinite because it defines the variables R^6 and R^7 which are not used in any of the formulas of claim 7. Claim 23 uses the abbreviations "Ln" and "Ch". However, these abbreviations are not defined previously in the claim, and are not art-recognized standard abbreviations.

3. Claims 6, 28, and 35 are objected to because of the following informalities: At claim 6, page 13 of the amendment filed March 18, 2004, second-to-last line, "5-7" should be subscripts. At claim 28 (see, e.g., line 17; page 28 of the amendment, lines 2, 5, 11, and 14; and page 29, line 18) and claim 35, " L_n " and " C_h " need to be changed to "Ln" and "Ch". Appropriate correction is required.

4. The effective filing date of instant claims 6-11, 15, 17, 20-22, 24-46, 48, 49, 57-59, 65-67, 69-71, 75, and 77 is deemed to be February 14, 2001, the filing date of the instant application. These claims are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,627 because the '627 provisional application,

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under the test of 35 U.S.C. 112, first paragraph, for example, does not disclose targeting moieties which are matrix metalloproteinase inhibitors having a $K_i > 100$ nM (compare page 9, lines 3-12, and claim 1 of the provisional application; note also that page 1, lines 1-21, of the provisional application does not disclose compounds with 2-10 targeting moieties and does not disclose the use of chelators); does not disclose R^5 , R^1 , R^2 , R^8 , R^9 , $R^{9'}$, R^{10} , and R^{11} groups which optionally comprise a bond to the chelator; does not disclose R^1 and R^2 forming the ring system of instant claim 6, page 10, lines 20-23; does not disclose the optional R^{27} substituents of instant claim 6, page 11, line 11, and claim 7, page 13, line 14; does not disclose linking groups where W^1 or W^2 are $(OCH_2CH_2)_{76-84}$; does not disclose the second and third formulas of claim 20; does not disclose that the A groups of claim 20 can be N, NR^{26} , NR^{19} , $-S(Pg)$, or a bond to a targeting moiety; does not disclose that R^{23} can be a bond to a targeting moiety; does not disclose the R^{26} group of claim 25 which is a bond to metals in general or which is a hydrazine protecting group; does not disclose the compound recited at claim 46, page 43, last line; does not disclose the radiosensitizers of claims 57, 59, 75, and 77; and does not disclose each of the diseases and conditions recited in instant claims 69-71. Note that unless a claim is limited exclusively to subject matter recited in a parent application, the claim is not entitled to the benefit of the filing date of the parent application. See MPEP 201.11(VI).

The effective filing date of instant claims 1, 4, 5, 12-14, 16, 18, 19, 23, 47, 50-56, 60-64, 68, 72-74, 76, and 78 is deemed to be February 15, 2000, the filing date of provisional application 60/182,627. These claims are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the '627 provisional application because the '627 provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

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5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 6-11, 15, 17, 20-22, and 24-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Carpenter, Jr. et al (U.S. Patent No. 6,656,448). Carpenter, Jr. et al teach the same compounds recited in Applicants' claims 46 and 50, and teach their combination with a pharmaceutically acceptable carrier and a stabilizer and optionally in kit form. See, e.g., column 20, line 18 - column 21, line 30; column 21, lines 57-60; column 22, lines 5-11; and column 43, lines 52-59. Although Carpenter, Jr. et al intend to complex a diagnostic metal rather than a cytotoxic radioisotope with their chelating groups and intend to use their compounds diagnostically rather than therapeutically, an intended use does not impart patentability to compound claims which are otherwise anticipated by the prior art.

The effective filing date of the subject matter disclosed by Carpenter, Jr. et al and relied upon by the examiner in the above rejection is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,712 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses said subject matter. See, e.g., page 23, line 28 - page 26, line 9; page 76, lines 25-30; and Examples 1-12, 15, and 16. Because the inventorship of Carpenter, Jr. et al is different than the instant application and because Carpenter, Jr. et al has an earlier effective filing date than the instant application, Carpenter, Jr. et al is available as prior art against the rejected claims under 35 U.S.C. 102(e). See MPEP 706.02(f)(1), Example 2, and MPEP 2136.03(III).

7. Claims 20, 69, and 70 are rejected under 35 U.S.C. 102(e) as being anticipated by Liu (U.S. Patent Application Publication 2002/0004032). Liu teaches compounds comprising

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macrocyclic chelants linked to a targeting moiety which can be a matrix metalloproteinase inhibitor. Cytotoxic radioisotopes such as ^{186}Re and ^{188}Re can be complexed with the macrocyclic chelants. The compounds can be in kit form including stabilizers and pharmaceutically acceptable carriers. The compounds are used to treat, e.g., cancer, restenosis, diabetic retinopathy, and macular degeneration. See, e.g., paragraphs [0336], [0337], [0404], [0405], [0408], and claim 21.

The effective filing date of the subject matter disclosed by Liu and relied upon by the examiner in the above rejection is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/195,234 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses said subject matter. See, e.g., page 40, lines 13-27; page 66, lines 2-10; page 66, line 27- page 67, line 4; and claim 18.

8. Claims 57-59, 65-67, 71, 75, and 77 are rejected under 35 U.S.C. 103(a) as being obvious over Liu (U.S. Patent Application Publication 2002/0004032) as applied against claims 20, 69, and 70 above, and further in view of MacPherson et al (U.S. Patent No. 5,646,167) and the European Patent Application 649,658. Liu does not teach combining the compounds with other chemotherapeutic agents or radiosensitizers. MacPherson et al teach combining matrix metalloproteinase inhibitors with other anticancer agents such as methotrexate in order to treat tumors such as human prostate, breast, lung, and colon tumors. See, e.g., column 1, lines 54-55; column 19, lines 57-64; column 20, lines 23-25. The European Patent Application '658 teaches including compounds such as 3-amino-1,2,4-benzotriazine-1,4-dioxide with chemotherapeutic agents in the treatment of solid tumors in order to increase the cytotoxicity of the chemotherapeutic agents. The tumors to be treated include breast and colorectal tumors and

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lymphomas. See, e.g., page 4, lines 32-38, and claims 1 and 3. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the matrix metalloproteinase inhibitors of Liu with the active agents of MacPherson et al and the sensitizers of the European Patent Application '167 because it is routine in the cancer art to use combinations of anti-cancer agents, because MacPherson et al show that it is known to combine matrix metalloproteinase inhibitors with other known therapeutic agents in order to treat cancer, and because the use of multiple agents having different mechanisms of action would have been expected to increase the chances that a cancer would be successfully treated.

9. Applicant's arguments filed March 18, 2004 have been fully considered but they are not persuasive.

The rejection of certain of the claims over Carpenter, Jr. et al (U.S. Patent No. 6,656,448) is maintained. Applicants have amended, e.g., independent claim 1 so that it is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,627.

Accordingly, Carpenter, Jr. et al is no longer prior art against instant claim 1 and the rejection of claim 1 over Carpenter, Jr. et al is withdrawn. However, many of the claims, including claims which are dependent upon claim 1, are not entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application '627, and Carpenter, Jr. et al remains available as prior art under 35 U.S.C. 102(e) against these claims. That an independent claim is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of a provisional application does not mandate a conclusion that all claims dependent upon the independent claim are entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application.

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Claims 20, 69, and 70 remain rejected under 35 U.S.C. 102(e) over Liu (U.S. Patent Application Publication 2002/0004032). These claims are not entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,627 for the reasons set forth in paragraph 4 above, and accordingly Liu is available as prior art against these claims under 35 U.S.C. 102(e). A showing of common ownership does not disqualify as prior art an anticipatory reference which is applied under 35 U.S.C. 102(e).

Claims 57-59, 65-67, 71, 75, and 77 remain rejected under 35 U.S.C. 103(a) over Liu (U.S. Patent Application Publication 2002/0004032). These claims are not entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,627 for the reasons set forth in paragraph 4 above, and accordingly Liu is available as prior art against these claims under 35 U.S.C. 102(e). Applicants' statement of common ownership set forth at page 53 of the response filed March 18, 2004 is insufficient to disqualify Liu as a reference under 35 U.S.C. 103(a) because the statement does not make clear when Liu was assigned to Dupont Pharmaceuticals, when the instant invention was assigned to Bristol-Myers, and whether Dupont Pharmaceuticals was a part of Bristol-Myers at the time this invention was made. Note, for example, there is no indication in Applicants' statement that this invention was ever subject to assignment to Dupont Pharmaceuticals. Note also that current office assignment records show that Liu is not currently assigned to Dupont Pharmaceuticals, and that the instant claimed invention was not assigned to Bristol-Myers at the time the instant claimed invention was made (the execution dates of the assignments to Dupont Pharmaceuticals are in February and March 2001, after the filing of this application). Clarification of Applicants' statement of common ownership is required.

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If Applicants submit a statement of common ownership which is effective to disqualify Liu (U.S. Patent Application Publication 2002/0004032) as prior art under 35 U.S.C. 103(a), then it will be necessary for the examiner to make the corresponding rejection over Liu (U.S. Patent Application Publication 2002/0098149), which was cited in the previous Office action as being essentially duplicative of Liu (U.S. Patent Application Publication 2002/0004032). In order to expedite prosecution of this application, it is suggested that Applicants submit a statement of common ownership over Liu (U.S. Patent Application Publication 2002/0098149) in response to this Office action.

10. Claims 1, 4, 5, 19, 47, 51-56, 60-64, 68, 72-74, and 78 are allowed. Claims 12-14, 16, 18, 48-50, and 76 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 23 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

11. In their response to this Office action, Applicants are requested to supply copies of the signed declaration filed July 2, 2001 and the Office action mailed December 12, 2001. Copies of these papers are missing from the image file wrapper, and the examiner would like to ensure that a complete record of the application is present in the IFW.

Applicants did not respond to this request in their latest communication.

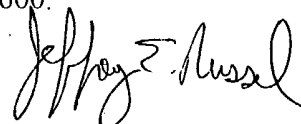
12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (571) 272-0961. The fax number for formal communications to be entered into the record is (703) 872-9306; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
April 26, 2004